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A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration, and immunity

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Abstract *N,N*-dimethyltryptamine (DMT) is classified as a naturally occurring serotonergic hallucinogen of plant origin. It has also been found in animal tissues and regarded as an endogenous trace amine transmitter. The vast majority of research on DMT has targeted its psychotropic/psychedelic properties with less focus on its effects beyond the nervous system. The recent discovery that DMT is an endogenous ligand of the sigma-1 receptor may shed light on yet undiscovered physiological mechanisms of DMT activity and reveal some of its putative biological functions. A three-step active uptake process of DMT from peripheral sources to neurons underscores a presumed physiological significance of this endogenous hallucinogen. In this paper, we overview the literature on the effects of sigma-1 receptor ligands on cellular bioenergetics, the role of serotonin, and serotoninergic analogues in immunoregulation and the data regarding gene expression of the DMT synthesizing enzyme indolethylamine-*N*-methyltransferase in carcinogenesis. We conclude that the function of DMT may extend central nervous activity and involve a more universal role in cellular protective mechanisms. Suggestions are offered for future directions of indole alkaloid research in the general medical field. We provide converging evidence that while DMT is a substance which produces powerful psychedelic experiences, it is better understood not as a hallucinogenic drug of abuse, but rather an agent of significant adaptive mechanisms that can also serve as a promising tool in the development of future medical therapies.

Keywords *N,N*-dimethyltryptamine · Indolethylamine-*N*-methyltransferase · Sigma receptors · Oxidative stress · Immunoregulation · Carcinogenesis

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Introduction

N,N-dimethyltryptamine (DMT) is a naturally occurring methylated indolealkylamine possessing potent psychotropic properties (Barker et al. 2012). This indole alkaloid is widespread in nature and abundant in plants such as *Diplopterys cabrerana* and *Psychotria viridis*, which are used in preparation of sacramental psychoactive decoctions such as *yage* and *ayahuasca* (Luna 2011). In addition to its ubiquitous presence in the plant kingdom, DMT has also been detected in animal tissues and is considered to act as an endogenous trace amine (Wallach 2009). Trace amines (such as octopamine, phenylethylamine, tyramine, tryptamine, and its derivatives) are generally present at low concentrations and accumulate in high amounts only in certain locations and under special circumstances—for

example, when the catabolic mechanisms are inhibited (Su et al. 2009), or under stressful conditions (Beaton and Christian 1977). The significance of the extensive natural presence of DMT and the biological role it fulfills remains unclear.

Biosynthesis and biodistribution of DMT

Structurally, DMT is related to the neurotransmitter serotonin, the hormone melatonin, and other psychedelic tryptamines such as bufotenin and psilocin. The biosynthesis of DMT starts from the decarboxylation of the essential amino acid tryptophan to tryptamine, followed by transmethylation through the actions of the enzyme indolethylamine-*N*-methyltransferase (INMT). Using *S*-adenosyl methionine, INMT catalyzes the addition of methyl groups to tryptamine, a process resulting in the end product indolealkylamine (Barker et al. 1981). The enzymatic activity is regulated in vivo by dialyzable endogenous inhibitors (Lin et al. 1974; Marzullo et al. 1977). INMT is widely expressed in the body with the highest levels in the lungs, thyroid, and adrenal gland. Intermediate levels are found in placenta, skeletal muscle, heart, small intestine, stomach, pancreas, and lymph nodes; it is localized densely at the anterior horn of the spinal cord (Mavlyutov et al. 2012; Thompson et al. 1999).

Since INMT is predominantly present in peripheral tissues, its main physiological function is supposedly non-neural (Karkkainen et al. 2005). While the brain is not known to have significant amount of INMT (with the exception of the pineal gland [Cozzi et al. 2011]), an active transport of DMT across the blood–brain barrier (Cohen and Vogel 1972; Sangiah et al. 1979), nevertheless, suggests that peripheral synthesis may influence central nervous functions. The active uptake of DMT into the brain makes it entirely different from most neurotransmitters, which do not have significant blood–brain barrier permeability and do not act on the central nervous system from a distance. The same tissues that contain INMT often contain enzymes that catabolize DMT. Only a fraction of intracellularly formed DMT is released to blood, and consequently is inconsistently detected either there or in the original tissue sample (Karkkainen et al. 2005). Therefore, a puzzling question arises: How can the peripherally synthesized DMT reach the brain in a significant enough amount to act on it?

Accumulation and storage of DMT

Based on evidence from past studies and some more recent findings, a three-step mechanism is postulated that would allow DMT to reach high local concentrations within neurons. The first step entails crossing the blood–brain barrier by an uptake across the endothelial plasma membrane according to reports that described the accumulation of DMT and other tryptamines in the brain following peripheral administration (Barker et al. 1982; Sitaram et al. 1987; Takahashi et al. 1985; Yanai et al. 1986). The second step involves the serotonin uptake transporter located on the neuronal surface. This action is followed by a third one, which is the DMT's facilitated sequestration into synaptic vesicles from the cytoplasm by the neuronal vesicle monoamine transporter 2 (Cozzi et al. 2009). After its neuronal uptake, DMT can act at intracellular modulators of signal transduction systems (see below) or remain stored in vesicles for up to at least 1 week and available to be released under appropriate stimuli (Vitale et al. 2011). The latter team has found that DMT had not only entered the brain rapidly, but also stayed there. The injected amount crossed the blood–brain barrier within 10 s after intravenous administration and was only partially excreted in urine. It was different in the case of tryptamine which had also gone through a rapid brain uptake, but had been fully excreted by 10 min after injection. In contrast, DMT persisted in the brain beyond 48 h and was still detected at day 7 after injection. There were no traces of either DMT or any other metabolite in the urine at 24 h after injection. These authors concluded that DMT was not removed from the brain beyond a certain point, and even after a complete clearance from the blood, it was still present in the central nervous system.

In essence, DMT is passing through three barriers with the help of three different active transport mechanisms to be compartmentalized and stored within the brain. In this manner, high intracellular and vesicular concentrations of DMT can be achieved within neurons. The outlined stages of uptake reveal that considerable physiological effort is exerted for the accumulation and storage of DMT and suggest that it has vital importance, since only a few compounds such as glucose and amino acids are known to be treated with similar priority. These extensive specialized processes would not have evolved to target a toxic compound or merely because of the psychedelic effects of DMT.

DMT as an endogenous hallucinogen

Szara (1956) reported first the psychoactive effect of DMT in humans within research settings. Shortly thereafter, Axelrod (1961) demonstrated the occurrence of DMT in the rat and human brain, leading him and others (Christian et al. 1977; Hollister 1977) to propose that DMT is an endogenous hallucinogen. As research progressed, it was

noted that DMT may fulfill the criteria for consideration as a neurotransmitter or a neuromodulator per se (Barker et al. 1981). The vast majority of the initial research into the reasons for the presence of psychoactive alkylamines in the human body has sought their involvement in mental illness. While DMT is no longer recognized to be a causative ("schizotoxic") factor of schizophrenia, it is still widely considered to play a role in psychotic symptomatology (Daumann et al. 2010; Warren et al. 2012). Very little is known about the function of DMT in regulating normal human physiological processes, and the emphasis of research is mostly on understanding its psychedelic properties. Based on indirect evidence, DMT is supposed to be involved in naturally occurring altered states of consciousness, such as dreams, imagination, creativity, and spiritual experiences (Callaway 1988; Strassman 2001).

DMT as a scheduled drug

The lack of solid information on its biological importance and the overwhelming initial data on its hallucinogenic properties resulted in an official opinion that DMT is a neurotoxin, has no accepted medical use, and was consequently classified as a Scheduled One drug by the US Controlled Substance Act in 1970. Its psychoactive analogues (such as 5-methoxy-DMT) usually fall under the neurotoxin category in the chemical catalogs of pharmaceutical companies. Jacob and Presti (2005) oppose this view: "DMT is essentially non-toxic to body organs and does not cause physiological dependence or addictive behaviors. Thus, its classification as a dangerous drug is based primarily on socio-political reasons rather than clinical-scientific evidence" (p. 931).

The antagonistic official stance significantly impedes scientific research pertaining to this increasingly interesting molecule (Strassman 1995), which is not only neurochemically active but probably bioactive in the broadest sense. The main goal of this paper is to raise attention to other features of DMT, which go beyond its psychedelic effects and point toward a neuroprotective role instead of neurotoxic agency. Our proposal takes the *psychoheuristic* concept (Szara 1994) of this endogenous hallucinogen to another level.

DMT and serotonin receptors

Research has been inconclusive, thus, far on the receptors responsible for the psychoactive properties of DMT and other naturally occurring *N*-alkyltryptamines. It is generally believed that the hallucinogenic effects of DMT are mediated through serotonin receptors, particularly by the subtypes of the 5-HT_2 receptor, which was originally identified and typically labeled using the synthetic hallucinogen lysergic acid diethylamide (Bennett and Snyder 1976; McKenna and Peroutka 1989). DMT has agonistic affinity at the 5-HT_{2C} receptor, but this probably plays a less significant role—if any—in the psychedelic effect of DMT since tolerance develops at this site (Smith et al. 1998). On the other hand, tolerance to the subjective effects did not occur in clinical studies with DMT (Strassman et al. 1996). Agonist interactions at 5-HT_{1C} receptors, as opposed to 5-HT_2 receptors, have also been suggested to be a "common mechanism of action" of hallucinogenic agents (Pierce and Peroutka 1990). The 5-HT_{1A} agonistic potency of DMT is probably less relevant in this aspect since it works against DMT's hallucinogenic activity (Jacob and Presti 2005).

Nichols (2004) proposed that other receptor systems have to modify or add to the serotonin response of hallucinogens, since 5-HT_{2A} receptor action cannot fully account for the psychological effects of DMT. The involvement of various other serotonergic mechanisms has been proposed, including serotonin uptake transporters (Nagai et al. 2007) and monoamine oxidase enzymes (Reimann and Schneider 1993). However, certain behaviors (such as tremors, retropulsion, and jerking) and intracellular changes (e.g., phosphatidylinositol production) observed in rats treated with DMT do not involve the serotonin system or other monoaminergic pathways (Deliganis et al. 1991; Jenner et al. 1980).

DMT and the sigma-1 receptor

The latest identified target for DMT's action is the sigma-1 receptor (Sig-1R). The sigma receptor is an endoplasmic reticulum receptor comprising at least two subtypes: Sig-1R and Sig-2R (Hayashi and Su 2004; Quirion et al. 1992). The sigma site was originally thought to be an opiate receptor subtype, but now it is recognized as a non-opioid receptor residing specifically at the endoplasmic reticulum–mitochondrion interface. Sig-1Rs are intracellular modulators of signal transduction systems which influence endoplasmic reticulum–mitochondrial calcium transfer and regulate cellular bioenergetics, particularly under stressful conditions (Hayashi and Su 2007; Su et al. 2010). DMT is considered as a natural ligand, an endogenous agonist of the Sig-1R, and a sigma link is implicated in its psychedelic properties (Fontanilla et al. 2009). This is somewhat counterintuitive since many drugs—including non-hallucinogens—bind promiscuously to the Sig-1R with higher affinity than DMT. On the other hand, DMT's hallucinogenic characteristics are similar to other classical hallucinogens acting through serotonergic receptors and lacking Sig-1R potency. Moreover, the selective serotonin reuptake inhibitor, fluvoxamine is known to

have Sig-1R agonistic potential higher than DMT, yet—unexpectedly—works better in psychotic depression than antidepressants without this property (Stahl 2008). While the possibility that Sig-1Rs involved in hallucinations cannot be totally excluded at present, the results of a recent surge in sigma receptor research are pointing toward a landscape poor in psychedelic vistas, but opening up another horizon for DMT physiology. One can argue against the proposed functional role of DMT—to be outlined below—by pointing out that its Sig-1R-mediated effects require micromolar concentrations as seen in vitro (Fontanilla et al. 2009). In response, it has to be emphasized that the three-step transporter mechanism—described above—is the key process, which makes possible the accumulation of the DMT within neurons to reach relatively high levels for Sig-1R activation and to function as releasable transmitter in vivo (Vitale et al. 2011).

Effects of Sig-1R modulation

Sig-1Rs are critical regulators in neuronal morphogenesis and development via the regulation of mitochondrial functions and oxidative stress (Pal et al. 2012; Tsai et al. 2012; Tuerxun et al. 2010). In vivo and in vitro studies indicate that Sig-1R agonists are robustly protective in many ischemia, organopathy, and neurotoxicity models (Klouz et al. 2008; Mancuso et al. 2012; Penas et al. 2011; Tagashira et al. 2013; Vagnerova et al. 2006). In experimental conditions, when glutamate is used as an insult, the role of Sig-1R activation is controversial: in organotypic cultures of spinal cord slices, the Sig-1R agonist PRE084 defended motor neurons from glutamate excitotoxicity (Guzman-Lenis et al. 2009), but in cytotoxic assays using a HT-22 cell line, the Sig-1R antagonist haloperidol has turned out to be protective (Luedtke et al. 2012). Agonists of Sig-1R have been shown to exert neuroprotective effects by regulating intracellular calcium levels and preventing expression of pro-apoptotic genes in retinal ganglion cells (Tchedre and Yorio 2008). Sig-1R agonists have also been reported to preserve protective genes (such as Bcl-2) in a cerebral focal ischemia model (Yang et al. 2007; Zhang et al. 2012). Sig-1R activation has been shown to decrease intracellular calcium overload (Mueller et al. 2013) produced by both in vitro ischemia and acidosis (Cuevas et al. 2011a; Katnik et al. 2006). Katnik et al.'s (2006) findings indicate that tonic activation of sigma receptors or stimulation of sigma receptors upon induction of ischemia diminishes ischemia-induced elevations of intracellular calcium. Sigma receptors suppress multiple aspects of microglial activation and microglial deactivation attenuates neurotoxic effects (Cuevas et al. 2011b; Hall et al. 2009). Initial studies indicated that inhibiting Sig-1R prevents oxidative stress-induced cell death (Schetz et al. 2007), and subsequent investigations showed that Sig-1R stimulation protects against ischemic lesions (Ruscher et al. 2012). Moreover, Ruscher et al. (2011) found that Sig-1R activation induces changes in spine morphology and stimulates neurite outgrowth in primary neural culture. They concluded that Sig-1R activation induces neuronal plasticity, which is a long-term recuperative process that goes beyond neuroprotection. Similar neuronal plasticity changes were described by Tsai et al. (2009) and Kourrich et al. (2012).

In summary, accumulating evidences suggest that sigma receptors regulate cell survival and proliferation (Collina et al. 2013). DMT signaling through Sig-1Rs may shed light on its physiological relevance. Once inside a neuron—with the help of the three-step uptake mechanism discussed above—cytoplasmic DMT can interact with intracellular Sig-1Rs located in the mitochondrion-associated endoplasmic reticulum membrane (Hayashi and Su 2007). From vesicular storage, it can be released into the synapse in micromolar concentrations to stimulate cell-surface Sig-1Rs or to act on the intracellular Sig-1R of neighboring cells. The data presented suggest that DMT may regulate intracellular calcium overload and pro-apoptotic gene expression via activation of Sig-1R receptors. This mechanism can result in a DMT-mediated neuroprotection during and after ischemia and acidosis. The pathological consequences of hypoxic–anoxic damages can be further mitigated by DMT-facilitated Sig-1R dependent plasticity changes (Kourrich et al. 2012; Ruscher et al. 2011; Tsai et al. 2009).

One peculiarity of the indolethylamine-sigma link is the co-localization of INMT with Sig-1R at the C terminal of "C boutons" in motor neurons of the spinal cord. C terminals were found to modulate the excitability of anterior horn neurons, particularly under stressful conditions (Mavlyutov et al. 2012). Agonist activation of the Sig-1R at C terminals reduces motor neuron excitability and firing frequency. Motor circuits in the anterior horn of the spinal cord are the final neural arbiters of movement. The force and duration of muscle contraction is determined by motor neuron firing, which can be decreased by DMT action. One may hypothesize that by decreasing the energy consumption of skeletal muscles such an effect may be part of an adaptive process in hypoxic stress.

DMT in clinical death

The neuroprotective function of DMT can become very important after cardiac arrest when the main goal of physiological adaptation is to extend the survival of the brain. Based on the available evidence, we speculate that DMT functions in the following manner. In response to a life threatening situation or the physical signals of agony, the lungs can

synthesize large amount of DMT (by quick removal of the endogenous dialyzable INMT inhibitors without the need of new enzyme synthesis) and release it into the arterial blood within seconds. Once DMT enters blood circulation, it is relatively safe from degradation since extracellular, circulating monoamine oxidase enzymes deaminate only primary amines (McEwen and Sober 1967). Therefore, the tertiary DMT is not a substrate for the plasma monoamine oxidase and can reach the brain with minimal degradation.

As the heart has its last systolic contractions, the brain does not have too much time: It must use the multiple active transport mechanisms for taking DMT up from the blood, passing it through the neural membranes, and concentrating it in synaptic vesicles. A fast and even distribution is necessary, which can hardly be accomplished if the brain would be the source of DMT. The lung is a good candidate to fulfill this physiological role. As a part of a desperate recuperative process, the DMT uptake mechanism has the potential to keep the brain alive longer. Evidence for this role of DMT is found in the psychedelic feature of subjective reports provided after clinical death and near death experiences, which are phenomenologically similar to those of DMT. These observations suggest that DMT is very probably involved in the dying process (Strassman 2001).

Perinatal INMT activity

A similar protective mechanism might come useful in the perinatal period, especially during delivery. However, the lungs do not have a central position in fetal circulation, rather the placenta does. Perhaps, placental sources or a higher-than-adult INMT activity in the fetal lung compensate for the difference. Indeed, the activity of INMT in the rabbit lung is relatively high in the fetus, increases rapidly after birth, and peaks at 15 days of age. The activity declines to the mature level and remains constant thereafter (Lin et al. 1974). If it parallels with increased DMT synthesis, then Sig-1R mediated neuronal plasticity changes can be expected in the newborn. Systemic treatment with a highly selective Sig-1R agonist was protective against excitotoxic perinatal brain injury (Griesmaier et al. 2012) and ischemic neurodegeneration in neonatal striatum (Yang et al. 2010). In prenatal life, the expression of INMT in a gene network seems to be important for pregnancy success (Nuno-Ayala et al. 2012). While direct data is lacking in support of this hypothesis, each step is easily testable.

Sigma and serotonin receptors in immunoregulation

As an endogenous ligand of Sig-1R and serotonin receptors, DMT may also play a significant role in the regulation of immune processes and tumor proliferation. Sigma receptors exist not only in the peripheral and central nervous system, but are also expressed by many cells of the immune system (Gekker et al. 2006) suggesting their involvement in immune functions. In addition, Sig-Rs have been shown to be expressed in many cancer tissues from both neural and non-neural origins (Aydar et al. 2004; Megalizzi et al. 2007). Sig-1R agonists have the ability to reduce pro-inflammatory cytokines and enhance the production of the anti-inflammatory cytokine IL-10 (Derocq et al. 1995). In pathological conditions where a cytokine imbalance is present, similar effects were suggested as being useful (Bourrie et al. 2004).

Through effects at the 5-HT_{2A} receptor, DMT can exert a strong impact on the effector functions of immunity. There is a vast literature about the immunological influence of serotonin (Ahern 2011; Cloez-Tayarani and Changeux 2007). It is well-known that serotonin has multiple effects on cellular immune functions that are critical in the elimination of pathogens or cancer cells, such as antigen presentation and T cell polarization (Leon-Ponte et al. 2007; O'Connell et al. 2006). An in vivo study by Dos Santos et al. (2011) found that the DMT-containing *ayahuasca* increased the level of blood-circulating NK cells in humans with concentrations as low as 1.0 mg DMT/kg body weight. Furthermore, in a pilot study, we observed a significant increase in the levels of secreted interferon-gamma and interferon-beta in cultures of human NK cells and dendritic cells after DMT administration in vitro. This increase was consistent with our further findings showing an increase in type I and type II interferon gene expressions in these cells, but interestingly was not associated with alterations in the mRNA and protein levels of inflammatory cytokines (Szabo et al. unpublished results). Since interferons are not only antiviral agents, but also considered as potent anticancer factors (Caraglia et al. 2009; Gonzalez-Navajas et al. 2012; Szabo et al. 2012; Windbichler et al. 2000), here, we hypothesize that DMT-modulation of the immune response may be beneficial in contributing to or resulting in a much better elimination of infected or malignantly altered self cells. Indeed, modern pharmacological strategies target the modulation of interferon response to enhance the effectiveness of cancer therapy (Caraglia et al. 2009; Lasfar et al. 2011; Watcharanurak et al. 2012).

INMT expression in cancer

The association of the down-regulation of INMT gene (*Inmt*) expression with cancer was reported by several groups (Kopantzev et al. 2008; Larkin et al. 2012). According to these results, *Inmt* was identified as a candidate gene in prevention

of cancer progression. Its expression showed a dramatic decrease in the recurrence of malignant prostate (Larkin et al. 2012) and lung cancers (Kopantzev et al. 2008). One of the possible regulating roles of INMT (via its product DMT) in carcinogenesis could be a direct tumor suppressor effect. However, this is unlikely since it has no known impact on the tissue dynamics of differentiating embryonic or proliferative adult tissues per se (Nuno-Ayala et al. 2012). On the other hand, DMT synthesized locally by INMT may represent a significant stimulus for tissue resident immune cells in the tumor environment. It can also act as a non-dispensable defensive factor in the protection of higher vertebrate tissues by controlling the cytokine response of local immune cells. As mentioned above, DMT can increase the level of circulating NK cells (a natural source of interferon-gamma) in vivo and also initiate the production of type I and type II interferons by human dendritic cells. Thus, it is tempting to speculate that INMT has an important function by generating DMT to regulate, support, or complement the local immune responses, thereby preventing malignant processes.

INMT, via the control of DMT synthesis, may play role in the immune regulation of carcinogenesis. DMT—its biochemical product—can act as a non-selective agonist on serotonin receptors altering the effector functions and cytokine profile of immune cells leading to a tolerogenic, non-inflammatory state. On the other hand, serotonin receptor activation also plays a pivotal role in the immunological synapse between T cells and antigen presenting dendritic cells (Ahern 2011; O'Connell et al. 2006). We suggest that this very effect can stand in the background of the increased sensitivity to different cancerous transformations described by others (Kopantzev et al. 2008; Larkin et al. 2012), where the decrease in or lack of INMT activity might be consequently associated with a disrupted immune surveillance. Further studies are needed to clarify the exact role of INMT/DMT in this process. Since the down-regulation of *Inmt* expression may provide a massive survival benefit for cancer cells, it would be also important to examine the expression of *Inmt* in malignantly differentiated human tissues.

Conclusions

Explanations of the role of DMT in humans and nature remain elusive. Indeed, there is no comprehensive theory of DMT, a particular perplexing situation given the ubiquity of DMT across the plant and animal kingdoms (Barker et al. 2012). To place this situation in the context of scientific theories (e.g., Kuhn 1970), we may state that there is no existing scientific paradigm explaining the significance of DMT. While the dominant construal of DMT is that it belongs to hallucinogens, there is no explanation as to why humans (as well as other animals) have evolved an endogenous compound to produce hallucinations, especially since there are no reasons to expect such false perceptions of reality to be adaptive.

Our efforts, here, are not to be construed as a general theory or model of the role of DMT as a hallucinogen, but rather to present some examples of the potential role of DMT in adaptive biological processes. The outlined indirect—though converging—evidence and speculative cases of DMT function can orient research toward new directions and may offer components for a general framework regarding some of the fundamental roles of DMT in cellular adaptation. Instead of supporting a pathological model, these exemplars suggest a significant physiological function of DMT and provide a conceptual framework that is an alternative to the reigning "hallucinogen paradigm." The literature reviewed suggests that the traditional conceptualization of DMT as primarily a hallucinogenic or psychedelic compound is too biased and narrow in advocating a pathological role in humans and other species.

Our main conclusion is that DMT is not only neurochemically active, but also bioactive in general. Its sigma receptor actions are not so revealing for its psychedelic effects, but rather point to a universal regulatory role in oxidative stress-induced changes at the endoplasmic reticulum–mitochondria interface. This hypothesized physiological function provides adaptations in cases of general hypoxia (e.g., cardiac arrest or postnatal asphyxia) and in local anoxia (e.g., myocardial infarct or stroke). Moreover, DMT can positively influence immunoregulation and delay tumor recurrence. In essence, DMT probably is a natural participant of a biological recuperative-defense mechanism, and the medical ramifications of this possibility are vast. Obviously, supportive experimental data are necessary for advancing the outlined concepts.

Ingestion of exogenous DMT in combination with a reversible monoamine oxidase inhibitor—such as in the formula of *ayahuasca* preparation—can result in blood levels up to 1.0 mg/ml or more (Dos Santos et al. 2011). With the help of the detailed DMT transport mechanisms, this blood level can lead to local concentrations sufficient for Sig-1R (and serotonin receptor) mediated therapeutic effects. The assumed role of DMT in cell protection, regeneration, and immunity helps understanding why *ayahuasca* has been used traditionally in healing ceremonials among the indigenous and mestizo cultures of the Amazon Basin (Luna 2011). DMT or—more practically—some of its analogues may turn out to be useful in emergency medicine (cardiac arrest), cardiopulmonary resuscitation, intensive care (myocardial infarct), neurology (stroke), neonatal care (treatment of newborns with poor Apgar score), cardiac surgery, anesthesiology (protection against transient hypoxia), oncology, and hospice care.

These very bold recommendations are based on indirect evidence, and experimental verification is needed before any further consideration. Nevertheless, the evidence reviewed here indicates that there is already a substantial base of scientific findings providing support for a paradigm which construes DMT as an adaptive mechanism. We hopefully have presented in this paper convincing evidence that DMT is not best understood as a psychedelic drug, but rather a substance with adaptive features which provide a promising tool for the advancement of general medical practice.

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